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## RAT REACTION TO HYPOKINESIA AFTER PRIOR ADAPTATION TO HYPOXIA

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A study was made of 50-day hypokinesia with a preliminary month of adaptation /434\* to hypoxia and maintenance of the hypoxia training condition during the entire period of the hypokinesia effect. The prophylactic effect of prior hypoxia adaptation on the subsequent influence of hypokinesia was shown. The prophylactic effect of hypoxia adaptation showed itself in decreased reduction of body weight, in higher indices for red blood content, in heightened reactivity of the overall organism and central nervous system to acute hypoxia and in increased resistance of the skeletal muscles to modification as compared with these same indices in animals subjected to the effect of hypokinesia alone.

The materials we had obtained, correlated in survey articles and monographs [3-5,11], justified the conclusion, that a month's training in a decompression chamber with the use of the hypoxia program we had developed increased overall resistancy of the animals' organism. However in this context the resistance is relatively non-specific in character, since the animals become more resistant not only to hypoxia but to many other adverse factors as well.

It was also shown, that at the base of increased organic resistance there are adaptive processes not only in the functional systems (respiration, blood, blood circulation) but also at the cell level. It appears, that an increase in organic resistance is accompanied by a rise in the resistance of the central nervous system, myocardium, skeletal muscles and in the tissues there has been found a stimulation of oxidizing and anaerobic metabolism, increase in the activity of a number of enzymes, an increase in myoglobin content. There is also a change in the biochemical and biophysical properties of the erythrocytes and a change in the erythropoietic function of the bone marrow not only quantitatively but also qualitatively, etc. [4,5,10].

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Undoubted confirmation of the fact, that biochemical displacements in the tissues and cells play a real part in providing increased resistance of the total organism, is found not only in the concurrence of these processes at the moment of occurrence but also the results of experiments we have carried out on animals subjected to the effect of hypokinesia. A month of rigorous hypokinesia led to a ~~imp~~ in the resistance of the total organism, the central nervous system, the myocardium and the skeletal muscles and in these tissues there appeared to be a decrease in the glycolysis rate and myoglobin content. The change in the blood picture likewise took on a diametrically opposite direction [6,8,9].

Due to the results of the research described above we had to hypothesize, that prior hypoxia training might have a prophylactic effect also in respect to the subsequent action of hypokinesia. The present report is devoted to a clarification of this problem.

The experiments were conducted with a group of mongrel male rats subdivided /435 into 6 groups as shown in Table 1. In each series of experiments control rats, selected for matching weight, were observed simultaneously. To restrict movement the rats were put in individual box cages of plexiglass of a size that prevented the animals from moving. Only the front paws and head were allowed a degree of mobility for use in feeding. They were kept in the cages around the clock with food and drink ad libitum.

For purposes of hypoxia adaptation the animals were put in the decompression chamber 5 hours daily except for non-working days. On the first day altitude simulation was 2,500 m and was increased daily by 500 m until it reached 7,500 m. At that altitude the rats were trained until the month was up. Later in a longer experiment the rats were kept in the decompression chamber at 6,500 m for 3 hours on alternate days in order to prevent transfer training on the part of the rats merely adapting to hypoxia and the rats in the box cages. On the other hand the idea was to try to maintain the condition of hypoxia adaptation and on the other not overintensify the effect of stress under combined severe hypoxia and hypokinesia.

The test animals and controls were weighed each week. On the day after the end of the experimental period there was a determination of erythrocyte and hemoglobin content in the blood and then an evaluation of the resistance of the entire organism and central nervous system. 24 hours after these experiments the animals were decapitated and the resistance of the skeletal muscles measured. In order to assess overall resistance the animals were put singly under the hood of a non-ventilated chamber, about four liters in volume, where for 35-40 seconds the air was ra-

TABLE 1. GROUP DISTRIBUTION OF TEST RATS

Распределение подопытных крыс по группам

a №№ п/п	b Условные обозначения	c Содержание эксперимента	n
1	AГ <sub>30</sub> d	30-дневная адаптация к гипоксии	14
2	AГ <sub>80</sub> e	80-дневная адаптация к гипоксии	12
3	ГК <sub>30</sub> f	30-дневная гипокинезия	6
4	ГК <sub>50</sub> g	50-дневная гипокинезия	6
5	AГ <sub>80</sub> +ГК <sub>50</sub> h	80-дневная тренировка к гипоксии, из которой первые 30 дней до действия гипокинезии, и по- следние 50 дней — в комбина- ции с ней.	11
6	K <sub>30</sub> , K <sub>50</sub> , K <sub>80</sub> i	Контрольные животные к каждой группе . . . . .	27

- Key:
- a. Group number
  - b. Arbitrary designations
  - c. Experiment content
  - d. AH<sub>30</sub>: 30 day adaptation to hypoxia
  - e. AH<sub>80</sub>: 80 day adaptation to hypoxia
  - f. HK<sub>30</sub>: 30 day hypokinesia
  - g. HK<sub>50</sub>: 50 day hypokinesia
  - h. AH<sub>80</sub>+HK<sub>50</sub>: 80 day hypoxia training, of which first 30 days for  
effect of hypokinesia and last 50 days in  
combination with it
  - i. K<sub>30</sub>, K<sub>50</sub>, K<sub>80</sub>: control animals for each group

refied to simulated 12,500 m. In cases where the animal began to present a convulsive attack or if it was observed that the breathing ceased for a long time the "descent" was begun at once. Otherwise the animals were "brought down" after a 5 minute period spent under conditions of acute hypoxia. The time from commencement of the stay at an "altitude" of 12,500 m to beginning of the descent was characteristic of acute hypoxia tolerance or the gauge of overall resistance (the legitimacy of this last assumption is determined by all that was said in the introductory part of the article). In addition there was an assessment of the condition of the central nervous system on the basis of the type and rate of respiration, of the type of motor reactions and condition of muscular tonus and finally of the condition of the animal following the "descent". Thus determination of the animal's overall resistance simultaneously provided material for assessing the resistance of the central nervous system.

The judgment about the resistance of the skeletal muscles was made on the basis of the rate of loss of physiological excitability of the isolated gastrocnemius im-

mersed in a non-aerated Ringer solution with 5% ethyl alcohol. Every hour a liminal electric excitation was applied with rhythmic current for 1 microsecond. The gradual stepping up of the excitation served as a criterion for the rate of excitability loss by the muscular tissue, i. e. muscular resistance to injury. The test rats and controls were immersed in the same vessel in order to equalized experimental conditions.

#### Results of the Study

Changes in Body Weight. Table 2 presents changes of body weight in grams and percent of initial values. It is quite clear, that the mean body weight of the control rats rose uninterruptedly, indicating the normal condition of the experimental animals. In succession there was a reduction in the gain of body weight by the control rats in the I, II and III series of experiments and this is explained by differences in

Table 2. Mean changes ( $M \pm m$ ) of body weight of rats (in grams) following combined action of hypoxia and hypokinesia (series I), following adaptation to hypoxia (series II) and after hypokinesia (series III)

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a Серия экспериментов	b Опытные крысы				c Контрольные			
	d Исходный	e $\Delta G_{30}$	f $\Delta G_{30} + \Gamma K_{30}$	g $K_{30}$	d Исходный	g $K_{30}$	g $K_{30}$	
I	n 11	296 ± 4.9	244 ± 8.1	210 ± 6.7	n 7	203 ± 8.2	260 ± 9.5	307 ± 3.1
	% —	100	118	102		100	123	145
II	n 14	225 ± 5.1	239 ± 6.2	—	n 8	223 ± 9.5	269 ± 8.3	313 ± 5.3
	% 100	100	115	—		100	121	140
III	n 12	238 ± 5.0	276 ± 8.6	309 ± 9.3	n 6	236 ± 9.7	283 ± 11.5	313 ± 5.3
	% 100	100	116	130		100	111	122
	n 6	257 ± 11.5	213 ± 10.2	$\Gamma K_{30}$	n 6	268 ± 10.7	300 ± 11.2	327 ± 17.3
	% 100	100	83	—		100	112	122
	n 6	273 ± 12.6	232 ± 11.4	200 ± 11.1	n 6	268 ± 10.7	300 ± 11.2	327 ± 17.3
	% 100	100	85	73		100	112	122

Key: a. Experimental series  
 b. Test rats  
 c. Controls  
 d. Initial  
 e. hypoxia adaptation  
 f. hypokinesia  
 g. controls

initial weight: 170-235 g (series I), 195-260 g (series II) and 230-310 g (series III). The difference in the initial weight of the animals was determined by the time lapse created by the three series of experiences with the same general group of

rats. Thus the rats of series III were 80-90 days older than those in series I. It is well known, that the amount by which body weight increases is inversely proportional to the animals' age. However it is important to keep in mind, that the animals were not old in any of the three series. Maximum age was 9 months.

The data presented in the table are graphic testimony to the positive effect of prior adaptation to hypoxia in respect to the subsequent reaction of the organism to hypokinesia. Thus, if the body weight of the hypokinetic (HK) rats (series III) after 30 days ( $HK_{30}$ ) dropped 15-17% and after 50 days hypokinesia ( $HK_{50}$ ) dropped 27%, the 50 days hypokinesia following prior adaptation for a month to hypoxia (AH) and against that background (series I) resulted in only a 14% drop in body weight, i. e. nearly one half less than for the rats with 50 days hypokinesia without prior hypoxia adaptation.

Table 3. REACTION OF RATS TO ACUTE HYPOXIA (BEING AT "ALTITUDE" OF 12,500 M)

a Группы крыс	n	b Средняя длительность пребывания	c Количество крыс (в % от общего числа у которых были обнаружены)			
			d резкое беспо- коиство, судороги	e атония	f патология дыхания	g тяжелое дыха- ние после спуска
$K_{30}, K_{50}, K_{50}$	15	h 3 мин. 33 сек.	100	100	100	75
$HK_{30}$	6	3 мин. 11 сек.	100	100	100	100
$HK_{50}$	6	— 51 сек.	100	100	100	100
$AG_{30}$	14	5 мин. —	36	0	7	0
$AG_{50}$	12	5 мин. —	17	17	61	0
$AG_{50} + HK_{50}$	11	5 мин. —	73	55	73	9

Key: a. Groups of rats

b. Mean length of stay

c. Number of rats (in % of total) showing these symptoms:

d. Sudden restlessness, spasms

e. Atonia

f. Respiration pathology

h. minutes

g. Serious condition after "descent"

i. seconds

Resistance of Overall Organism and Central Nervous System. From Table 3 it is apparent that on the average the time spent by the rats at the simulated altitude of 12,500 meters after 30 days hypokinesia remained the same as in the control (3 min 11 sec and 3 min 33 sec respectively), but after 50 days hypokinesia it declined sharply (51 sec). /437

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The experiments showed, that out of 15 control rats 9 were capable of tolerating 5 minutes exposure at an "altitude" of 12,500 m without interruption of breathing or a general spasmodic attack. However after 50 days hypokinesia the longest survival time under conditions of acute hypoxia was 1 min 30 sec. For most rats in this group (4 out of 6) respiration ceased already during the "ascent" and at the moment when 12,500 m was reached clinical spasms developed and breathing was terminated. One rat died under these conditions and the other could only be revived by artificial respiration. Sudden restlessness, spasmodic twitching, complete atonia in the intervals between spasmodic movements, pathological respiration and a very serious condition following "descent" were observed in all the rats of this group without exception and appeared to a greater degree than in the animals after 30 days hypokinesia or in the control rats. The external appearance of animals with 50 days hypokinesia was evidence of deep seated pathology: their fur was ruffled and fell out in clumps.

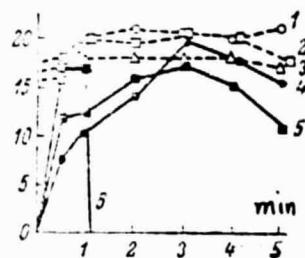


Fig. 1. Respiration rate of rats during stay at 12,500 m "altitude"  
Ordinate - 10 second breathing rate; abscissa - stay in minutes at  
"altitude" of 12,500 m. 1 - AH<sub>30</sub>, 2 - AH<sub>80</sub>+HK<sub>50</sub>, 3 - AH<sub>80</sub>, 4 - HK<sub>30</sub>,  
5 - control, 6 - HK<sub>50</sub>

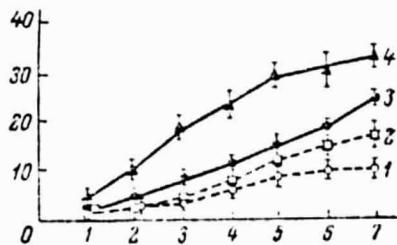


Fig. 2. Change in excitation threshold of isolated gastrocnemius muscles.  
Ordinate - excitation threshold in volts; abscissa - time in hours. 1 -  
AH<sub>30</sub> and AH<sub>80</sub>; 2 - AH<sub>80</sub>+HK<sub>50</sub>, 3 - control, 4 - HK<sub>80</sub>

A completely different picture was observed for animals who had also been submitted to 50 days hypokinesia but had been previously adapted to hypoxia. As is seen from Table 3, the stay of these animals at 12,500 m "altitude" was the same as that of the rats simply adapted to hypoxia over 30 or 80 days. All of them tolerated a 5 minute exposure.

The reaction of the central nervous system for rats in the AH<sub>80</sub>-HK<sub>50</sub> group was likewise more similar to the reactions of rats adapted to hypoxia alone than for the animals in the HK<sub>50</sub> group or the controls. Figure 1 shows respiration rate (at 10 second intervals) during a 5 minute exposure to 12,500 m altitude. It is clear, that it is the same as that of the rats adapted to hypoxia alone for 30 or 80 days as well as the rats with 50 days hypokinesia and prior adaptation to hypoxia (cf. curves 1, 2 and 3). Already at the moment of "ascent" to 12,500 m respiration was rapid and continued so during the 5 minute exposure. An entirely different picture was observed in the groups of control and hypodynamic rats (curves 4, 5, and 6). The chief distinguishing mark was the disappearance of respiration at the moment of "ascent" to 12,500 m and then, following a certain period of normalization, a fresh drop in the respiration rate. Breathing was particularly hard for the group of rats with 50 days hypokinesia (curve 6).

In respect to all other indices shown in Table 3 (absence of convulsions, type of respiration and muscle tone, general condition following "descent") the rats with prior adaptation to hypoxia and subsequent exposure to 50 days hypokinesia reacted to acute hypoxia in practically the same way as the animals well adapted to hypoxia and they differed strongly in their reactions from the controls or the animals who had been exposed to 50 days or even 30 days hypokinesia without prior adaptation to hypoxia.

Thus the resistance of the overall organism and central nervous system for rats with prior adaptation to hypoxia and then subjected to 50 days hypokinesia was somewhat lower than for animals adapted to hypoxia without hypokinesia but significantly higher than for control animals not subjected to any influences and likewise in comparison with rats subjected to 30 and especially 50 days hypokinesia without prior hypoxia adaptation. /438

Resistance of Isolated Skeletal Muscles. An analogous picture was observed in determining resistance of skeletal muscles. One may see from Figure 2, that the highest resistance (i. e. lowest rate of increase in the excitation threshold) is shown by the muscles of rats adapted to hypoxia over 30 or 80 days (curve 1), then by the

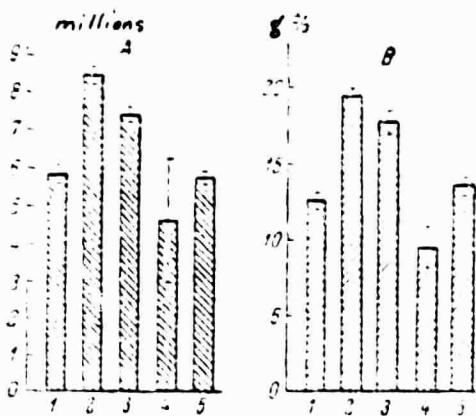


Fig. 3. Content of erythrocytes (A) in millions and hemoglobin (B) in g% in blood of rats. 1 - control, 2 - AH<sub>30</sub>, 3 - AH<sub>80</sub>, 4 - HK<sub>50</sub>, 5 - AH<sub>30</sub>+HK<sub>50</sub>

muscles of rats subjected to 50 days hypokinesia with prior adaptation to hypoxia (curve 2) and finally by the muscles of the control animals (curve 3). The lowest resistance to injury was noted for rats following 50 days hypokinesia (curve 4).

Red Blood Picture. It is seen from Figure 3, that hypoxia adaptation evoked the usual reaction on the part of the hematopoietic system: there was a rise in hemoglobin content and in the erythrocyte count, i. e. an increase in the blood's oxygen content. The lesser degree of increase in erythropoiesis in the group of rats with 80 days hypoxia training should be explained, it seems, by a decrease in the acuteness of the hypoxia effect following a 30 day period of training in the decompression chamber.

There is a very great point of interest in the values characterizing the oxygen content of the blood in rats following hypokinesia. In the case of 50 days hypokinesia we see a drop in both the erythrocyte count (not reliable due to the great scattering of values) and the hemoglobin content as compared with control values. In regard to the oxygen content of the blood in rats with 50 days hypokinesia exerting its influence after prior hypoxia adaptation and against that background there was no difference from the control values; in fact it surpassed the level of values for rats with 50 days hypokinesia exerting its effect in isolation. At the same time it cannot be ignored, that even in this case hypokinesia was a factor in

reducing the activity of erythropoiesis, since the blood oxygen content of animals in the AH+HK group was lower than for those who had hypoxia adaptation without the concurrent effect of hypokinesis. However it is important, that prior adaptation to hypoxia and extended training for hypoxia during the period of the action of hypokinesia appeared as a positive influence revealing itself in the fact, that the erythrocyte and hemoglobin content of the blood remained at a sufficiently high level.

#### Evaluation of Results

Summarizing generally it should be noted, that, as in our previous experiments, data was obtained testifying to the fact, that hypoxia adaptation increased the non-specific resistance of the organism. In this particular case it took the form of the animals' increased resistance to the action of hypokinesia.

In our view results of the use of hypoxia training as a prophylactic device may vary depending on the way it is used. In our previous research on prophylaxis against the radiation syndrome it was made clear, that a positive effect was noted only if hypoxia training preceded irradiation [1]. If, however, hypoxia training began immediately after irradiation, the radiation syndrome developed to an even more serious extent [2]. We explained this difference by the following circumstances. Inasmuch as hypoxia training raises the resistance of the organism, its tissues and cells, any adverse effect on such an organism is inevitably weakened. However if at the same time two extreme irritants, such as penetrating radiation and hypoxia (or hypokinesia and hypoxia), begin to act upon the organism, the initial stress condition of the organism is aggravated and the final type of reactions on the part of the organism may not be univocal.

The literature contains descriptions of experiments where at one and the same time rats began to be subjected to hypokinesia and training for hypoxia corresponding to an "altitude" of 5,000 and 7,000 m for a 30 day period [7]. In this context the finding was an increase in the blood's oxygen content, less pronounced influence of hypokinesia on the activity of proteolytic enzymes of the stomach and weakening in the disruption of mineral metabolism (the latter only with training to an "altitude" of 5,000 m). On the basis of the data obtained the authors were right in coming to the conclusion, that hypoxia training might be used as one of the means of defense against the adverse effects of hypokinesia.

However it appeared, that when there was a simultaneous combination of hypokinesia and training for hypoxia the animals' body weight decreased more than when they were subjected to hypokinesia alone. For these animals resistance to overload

decreased and resistance to acute hypoxia, just as in the case of exposure to hypokinesia alone, did not change, although it was 6.1 times higher for rats adapted to hypoxia without the influence of hypokinesia. Further it became clear, that when there was hypoxia training at an "altitude" of 7,000 m hypokinesia induced less severe disruption of mineral metabolism than when the only influence was hypokinesia.

All the facts enumerated above show, that there is a need for researching the optimal regimes for using hypoxia training as a defense against the pernicious effects of hypokinesia.

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